

**UNITED STATES DISTRICT COURT  
FOR THE NORTHERN DISTRICT OF OHIO  
EASTERN DIVISION**

**IN RE NATIONAL PRESCRIPTION  
OPIATE LITIGATION**

**This document relates to:**

*Track Three Cases*

**MDL No. 2804  
Case No. 17-md-2804  
Judge Dan Aaron Polster**

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**DECLARATION OF STEVEN N. HERMAN IN SUPPORT OF THE PHARMACY  
DEFENDANTS' MOTION TO EXCLUDE CERTAIN OPINIONS  
AND TESTIMONY OF DR. KATHERINE KEYES**

**EXHIBIT 34**



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## Addictive Behaviors

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# Psychoactive substance use prior to the development of iatrogenic opioid abuse: A descriptive analysis of treatment-seeking opioid abusers

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## HIGHLIGHTS

- Nearly half of the sample was first exposed to opioids through a prescription.
- It is very rare for one to be drug naïve prior to opioid exposure.
- Tobacco, alcohol and marijuana were nearly always used prior to opioid exposure.
- Over two-thirds still reported prior use of other psychoactive drugs.

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## ABSTRACT

Physicians are frequently thought to be a major source of opioids diverted for non-therapeutic purposes, largely because it is so difficult for them to discern which patients might abuse them. In this study we sought to determine whether those who were first exposed to an opioid through a physician's prescription, and subsequently developed a substance use disorder, had a history of using psychoactive drugs prior to abusing opioids. Patients entering one of 125 drug treatment programs across the country for opioid abuse were asked to provide detailed histories of psychoactive drug use prior to their initial opioid exposure. Nearly half (47.1%,  $N = 4493$ ) indicated they were first exposed to opioids through a prescription from their physician to treat pain. Of these, 94.6% indicated experience with at least one other psychoactive substance (mean =  $4.55 \pm 0.05$ ) prior to, or coincident with, their first exposure to an opioid from a physician. Alcohol (92.9%), nicotine and/or tobacco (89.5%), and marijuana (87.4%) were used by nearly all patients prior to, or coincident with, their first opioid prescription. If one excludes these drugs, 70.1% ( $N = 2913$ ) still reported some psychoactive drug use of licit or illicit stimulants (77.8%), benzodiazepines (59.8%) or hallucinogens (55.2%). Our results indicate that pain patients who developed a substance use disorder were rarely drug naïve prior to receiving their first opioid prescription. Rather, most have an extensive history of psychoactive drug use. As such, physicians should routinely ascertain complete licit and illicit drug histories in patients for whom they prescribe opioids.

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## 1. Introduction

Healthcare professionals who write opioid prescriptions for acute and, particularly, chronic pain have to consistently balance two often nagging considerations: First, since there is no tool to precisely gauge the presence or severity of the highly subjective experience of pain, physicians must exercise their professional judgment as to whether opioids are warranted or appropriate; and second, the more troubling point, it is very difficult for physicians to determine which patients are currently abusing opioids or are at risk for abuse (Harle et al., 2015; Kavukcu, Akdeniz, Avci, Altuğ, & Öner, 2015; Keller et al., 2012; Matthias & Bair, 2010). As a result, research has indicated that

physicians often unwittingly serve as a source of diversion of opioid drugs (Cicero, Surratt, Inciardi & Munoz, 2007; Inciardi, Surratt, Cicero, & Beard, 2009; Rigg, March, & Inciardi, 2010). While there are a number of screening instruments that are intended to aid physicians in making appropriate decisions about opioid management of pain and the potential for misuse, it is unclear how often any of these screeners are utilized (Jones et al., 2012; Meltzer, Hall, & Fins, 2013). What's more, most are relatively vague about one of the most important risk factors in vulnerable patients: a history of substance use.

Physicians often ask, as a matter of routine, about histories of alcoholism and nicotine dependence, and sometimes a catch-all 'other substance abuse,' but they rarely inquire about the specific use of other potent licit and illicit psychoactive drugs (e.g., stimulants and benzodiazepines) which may be relevant regarding a patient's risk for opioid misuse. While there have been some efforts to assess drug abuse

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histories in predicting non-medical opioid use in limited populations (Catalano, White, Fleming, & Haggerty, 2011), we are unaware of any large-scale systematic study that has examined full substance use histories in pain patients first exposed to an opioid through a physician's prescription who ultimately developed an opioid use disorder. To address this gap in the literature, we utilized an existing database of patients entering substance abuse treatment programs to retrospectively determine whether those who were first exposed to an opioid via a physician's prescription to treat pain were, in fact, drug naïve with respect to mood altering substances prior to the initial prescription.

## 2. Material and methods

In this study, we utilized data from the Survey of Key Informants' Patients (SKIP) Program, a key element of the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System, a comprehensive series of programs that collect and analyze post-marketing data on the abuse and diversion of prescription opioid analgesics and heroin (Cicero, Dart, et al., 2007; Dart et al., 2015). The SKIP Program consisted of a Key Informant Network with annual participation of more than 125 public and privately funded treatment centers, with a reasonable representativeness of the four census areas (*Region [SKIP %]*, 2014 *Census*]; Midwest [27.9%,21.2%], Northeast [15.5%,17.6%], South [33.6%,37.6%] and West [23.0%,23.6%]). Key Informants were asked to recruit clients over the age of eighteen who were entering their substance abuse treatment program with a primary diagnosis of opioid use disorder, as defined by DSM-V criteria. Clients were asked to complete an anonymous paper survey; an 85% response rate was attained. The survey packet included a \$20 Wal-Mart gift card and a self-addressed stamped envelope which, after completion, was used by the respondent to mail the survey (identified by a unique case number) directly to Washington University in St. Louis (WUSTL).

SKIP data were analyzed for 9540 respondents from the third quarter of 2010 until the second quarter of 2015 who endorsed past month abuse of at least one prescription opioid. Other than demographics, respondents were asked about their age and means of initial exposure to opioids; legitimate prescription from a doctor/dentist to treat pain or 'experimental' (get high, escape from life, curiosity, pressure from others, etc.). Lifetime use (therapeutically or non-therapeutically) and age of first use of ten other psychoactive substances (nicotine and/or tobacco, alcohol, marijuana, Ritalin and/or Adderall, amphetamines, methamphetamines, benzodiazepines, crack and/or cocaine, ecstasy or hallucinogens) were also surveyed, along with comparisons of each respondent's age of first opioid exposure to the ages of first use of other psychoactive substances used.

## 3. Results

Nearly half (47.1%,  $N = 4493$ ) of treatment-seeking prescription opioid abusers indicated they were first exposed to opioids through a prescription from their physician or dentist to treat pain. The sample included slightly more women (54.5%) than men, had an average age of 34.8 years old and were predominantly white (84.0%). Of these new initiates, 94.6% indicated they had experience with at least one other psychoactive substance (mean age of first substance =  $12.9 \pm 0.05$ ) prior to, or coincident with, their first exposure to an opioid from a physician (mean age of first opioid exposure =  $22.3 \pm 0.13$ ); just 4.2% indicated they were drug naïve, vis a vis any psychoactive drug use, prior to receiving their first prescription for an opioid analgesic medication (Fig. 1).

On average, patients who indicated they had used at least one other psychoactive substance had used a mean of  $4.55 (\pm 0.05)$  out of ten substances surveyed, prior to their initial use of an opioid. The types of drugs utilized are shown as frequency distributions in Fig. 2A and B. As can be seen, alcohol (92.9%), nicotine and/or tobacco (89.5%), and marijuana (87.4%) were initially used nearly all individuals prior to, or coincident with, their first opioid prescription. If one excludes the legally available tobacco and alcohol, and the semi-legal marijuana, 70.1% ( $N = 2913$ ) still reported some psychoactive drug use prior to, or coincident with, their first opioid prescription (Fig. 2A). As shown in Fig. 2B, the vast majority of these 2913 respondents used either licit (Ritalin and/or Adderall) or illicit (amphetamine, methamphetamine, crack and/or cocaine) stimulants (77.8%), followed by high rates of benzodiazepine use (59.8%) and any hallucinogen use, including ecstasy (55.2%).

## 4. Discussion/conclusions

The results of this study indicate that only 4% of those who experienced their first opioid via a physician's prescription were truly drug naïve. Rather, more than 95% had significant psychoactive drug experience prior to being prescribed their first opioid, a drug with well-established mood-altering effects. Two aspects of the data seem noteworthy: first, while nearly our entire sample had used alcohol, nicotine and marijuana before their initial opioid prescription, 70% had experience with other types of drugs; and, second, on average, four to five different types of drugs were used prior to initial opioid exposure from a prescription.

The high incidence rates of extraneous drug use prior to or coincident with first opioid abuse is striking, particularly licit and illicit drugs other than alcohol, nicotine and/or marijuana – stimulants, benzodiazepines and hallucinogens. While the use of benzodiazepines is

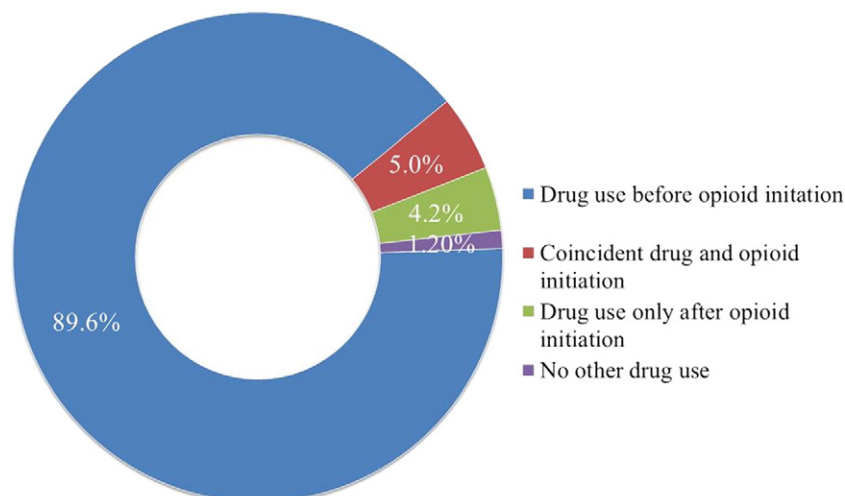
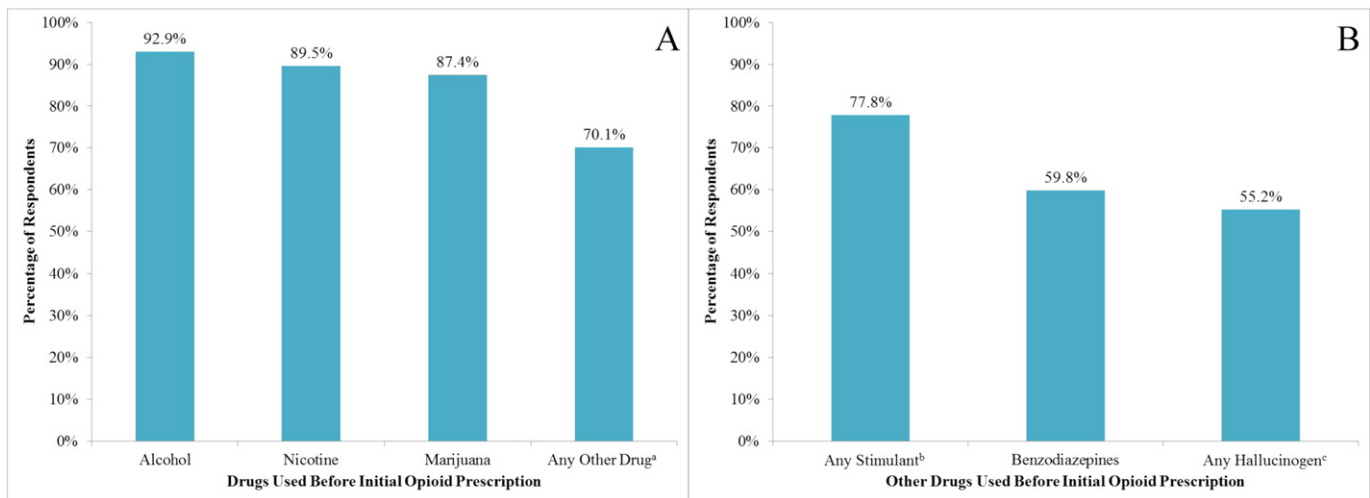


Fig. 1. Comparison of ages of first psychoactive drug use versus first use of an opioid for those initially exposed to an opioid through a physician's prescription ( $N = 4493$ ).



**Fig. 2.** A. Percentage of prescription-initiated SKIP respondents that used alcohol, nicotine, marijuana or other psychoactive drugs (stimulants, benzodiazepines and hallucinogens) prior to their initial exposure to an opioid (N = 4221). B. Breakdown of psychoactive drugs other than alcohol, nicotine and marijuana used by prescription-initiated SKIP respondents prior to their initial exposure to an opioid (N = 2913).

perhaps not surprising given that these drugs and opioids at least share some properties – sedation, relief of anxiety, etc. – what does seem unusual at first glance is how common the use of stimulants, and particularly, hallucinogens were prior to the first exposure to opioids. The most likely explanations of this finding are: First, opioids could serve a useful purpose in counterbalancing the mood swings produced by stimulants and/or hallucinogens; and, second, mood alteration produced by any psychoactive drug may encourage use of other drugs with such properties. Further research is needed to validate one or both of these postulates.

Although ours was a retrospective study without predictive modeling, our data do suggest, in agreement with the new CDC guidelines for the appropriate use of opioid analgesics (Dowell, Haegerich, & Chou, 2016), that physicians and pain management specialists should routinely ask patients that are candidates for opioid treatment about all of their drug use, not simply smoking and alcohol use, which is generally the norm. In this regard, more inclusive screeners should be developed that can collect and assess this information. Should evidence of prior drug use be found, opioids should either not be used at all or their therapeutic use patterns be carefully monitored. In this connection, when available, abuse-deterrent formulations that discourage insufflation and IV injection should also be considered.

The problem with these recommendations, of course, is that physicians and patients might be reluctant or embarrassed to discuss use of illicit substances or other prescribed medications (Keller et al., 2012), but none-the-less, given the common use of a substantial number of different psychoactive drugs – particularly stimulants, hallucinogens and benzodiazepines – prior to a patient's first use of an opioid, we would recommend that physicians overcome their reluctance and ask these sensitive questions. When in doubt, particularly if a physician is not confident about prescribing an opioid, we believe that asking for urine drug screens should seriously be considered both before and during chronic opioid therapy.

There are important limitations to our studies in addition to potential recall issues inherent in a retrospective study. Since ours is a treatment-based sample, our results might not be generalizable to all patients who receive opioid prescriptions, as it is known that prior substance use is a risk factor for opioid abuse. Furthermore, severity and frequency of use of all surveyed drugs were not assessed, and these factors could influence the degree of impact these drugs had on opioid abuse. Finally, while we did not assess whether Ritalin/Adderall and benzodiazepines were prescribed to respondents, these drugs, even in a treatment modality, produce alterations in mood/behavior.

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